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Prehospital Heparin Administration in Patients with Stemi Undergoing Primary PCI: Heparin Stemi Randomized Controlled Trial

Running title: *Fister et al.; Heparin Pretreatment in STEMI Patients Undergoing PCI*

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Abstract

Background: Primary PCI is the preferred reperfusion strategy in patients with ST-elevation myocardial infarction (STEMI). We investigated benefits and safety of pretreatment with unfractioned heparin (UFH) in STEMI referred to primary PCI.

Methods: Our single-center, open-label, randomized controlled trial assigned STEMI with ≤6 hours of symptom duration either to 70-100 IE/kg bolus of UFH at first prehospital medical contact (FMC) plus supplemental dose before PCI adjusted to activated clothing time ≥250 seconds or to control group undergoing standard UFH at the time of PCI. Primary efficacy endpoint was TIMI 2-3 flow in infarct related artery (IRA) at initial coronary angiography. Primary safety endpoint was BARC 3-5 bleeding during the index hospital stay.

Results: From March 2022 to February 2025, 298 patients were randomized to UFH pretreatment and 295 to the control group. Both groups were comparable in age, gender, risk factors, previous cardiovascular events and median delay from symptoms to coronary angiography (145 min vs 150 min; p=0.814). Median time from UFH pretreatment to coronary angiography was 60 min (25th and 75th IQR 47 - 55 min). TIMI 2-3 in IRA was documented in 43% in UFH pretreatment and 27% in control groups (RR 1.59 [95% CI 1.27-1.98]; p<0.001) without significant difference in BARC 3-5 bleeding (2.4% vs 2.0%; RR 1.16 [95% CI 0.39-3.45]; p=0.789).

Conclusions: In patients with STEMI undergoing primary PCI in a mature STEMI network, pretreatment with UFH at FMC was associated with an absolute 16% increase in IRA patency without causing excessive bleeding.

Clinial Trial Registration: ClinicalTrials.gov: NCT05247424, 02/18/2022

Key Words: heparin; pretreatment; STEMI; primary PCI

Non-standard Abbreviations and Acronyms:
UFH – unfractionated heparin
FMC – first medical contact
IRA – infract related artery
TIMI flow – Thrombolysis in Myocardial Infarction
BARC – Bleeding Academic Research Consortium
ACT – activated clotting time

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Clinical Perspective

What is new?

- In patients with STEMI reffered for primary PCI, intravenous bolus of UFH (70-100 IU/kg) administered at the first prehospital medical contact increased patency of infarct related artery by absolute 16%.
- Increased patency of infarct related artery was achieved without excessive bleeding.

What are the clinical implications?

- The HEPARIN STEMI randomized study supports routine UFH administration at the first medical contact in patients with STEMI reffered for primary PCI.
- Prehospital UFH administration is effective, safe, cheap and widely available.

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Introduction

Primary percutaneous coronary intervention (PCI) nowadays represents a standard reperfusion strategy in patients with ST-elevation myocardial infarction (STEMI)[1,2]. Since patent infarct related artery (IRA) at initial coronary angiography is associated with improved outcome[3], several pharmacological agents including unfractioned heparin (UFH), bivalirudin, GP llb/llla inhibitors and oral $P2Y_{12}$ inhibitors have been attempted with mixed success [4–10]. Most recently, subcutaneous pretreatment with a novel glycoprotein IIb/IIIa inhibitor, zalunfiban, was also found to improve IRA patency but was associated with increased mild to moderate bleeding.[11]

Pretreatment with UFH, which is nowadays a predominant intravenous anticoagulant during primary PCI for STEMI, was first investigated in DANAMI-2 trial.[12] Following a bolus of 10.000 IU of UFH on the way to primary PCI, a 32% IRA patency rate was documented at first coronary angiography. This is in accordance with several retrospective observational studies ~~which~~ demonstrating improved IRA patency and better clinical outcome[7,8,10]. In contrast, HEAP randomized trial[9] in which high UFH dose (300 IE/kg) was compared to low dose or no UFH did not increase IRA patency (22% vs 21%; p>0.1) and was associated with a strong trend toward increased need for transfusion (10% vs 6%; p=0.07). Very recently, HELP-PCI randomized study performed by Chinese investigators demonstrated that UFH pretreatment significantly improved TIMI 3 flow at initial coronary angiography from 17.6% to 23.6%[13]. In this study, however, less than 5% of patients received prehospital UFH at the first medical contact (FMC) while the rest of the patients were pretreated later on the way to primary PCI.

In the present study, we investigated UFH pretreatment at the FMC in a contemporary high volume primary PCI network characterized by systematic prehospital electrocardiographic STEMI diagnosis and direct transfer to a single high volume »24-7« primary PCI center [1].

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Methods

Data availability statement

Data, analytic methods and study materials will be available to other researchers upon request by contacting the first or the last author of the study.

Study design

The "HEPARIN-STEMI" was investigator-initiated single-centre, open-label, randomized controlled trial (NCT05247424) funded by the University Medical Center Ljubljana (Grant No. 20220075). The trial was approved by the National Ethics Committee (No. 0120-591/2021/3) which granted a waiver for informed consent at the time of randomization. Written informed consent was therefore obtained during hospitalization with timing depending upon the mental condition of the patient. In case of death, National Ethics Committee granted approval for data utilization without patient consent. Data were collected by the investigators and analyzed by independent statistician (Supplementary appendix). Manuscript was drafted by the first and the second author and edited by coauthors who agreed to manuscript submission and vouch for the accuracy and completeness of the data. A detailed protocol of the study has been previously published[14].

Patients

The HEPARIN-STEMI study enrolled consecutive patients with STEMI referred for primary PCI within the Ljubljana STEMI network[15]. Patients were >18 years old, had obvious STEMI in 12-lead electrocardiogram (ECG)[8] recorded at the prehospital FMC and symptom duration of ≤6 hours. Pregnant women, comatose survivors of out-of-hospital cardiac arrest and patients in cardiogenic shock were excluded.

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Randomization

After documenting STEMI in 12-lead ECG recorded at prehospital FMC, emergency physician informed acute cardiac care physician at the Center for Intensive Internal Medicine, University Medical Center Ljubljana (Slovenia) and sent the 12-lead ECG. After confirming STEMI diagnosis and fulfillment of inclusion criteria, patient was randomized 1:1 to either UFH pretreatment administered at FMC on the field or control group without UFH pretreatment. Randomization was performed using random permutated blocks via secure online randomization service (www.sealedenvelope.com).

Procedures

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At prehospital FMC, all patients received acetylsalicylic acid (250-500 mg per os) and no P2Y12 inhibitor. Patients randomized to UFH pretreatment received 70-100 IE/kg intravenous bolus[1] at prehospital FMC plus supplemental dose after initial coronary angiography and before primary PCI which was adjusted to activated clotting time (ACT) of ≥250 seconds. Control group received 70-100 IE/kg UFH bolus after initial coronary angiography and before primary PCI. Primary PCI was performed by one of the attending interventional cardiologists at the University Medical Center Ljubljana (Slovenia) who was blinded to the group assignment. Eptifibatide or cangrelor were given only during primary PCI at the discretion of the interventional cardiologist. The patients were then admitted to cardiac intensive care unit for monitoring and further care. Repeat 12-lead ECG was recorded immediately on admission.

Outcomes

All coronary angiograms were evaluated by an experienced interventional cardiologist who was blinded to group assignment.

Primary efficacy endpoint was TIMI flow grade 2 or 3 in IRA at initial coronary angiography. Primary safety endpoint was occurrence of BARC 3-5 bleeding during the index hospital stay[16].

Secondary endpoints were postprocedural TIMI 3 flow, early ST-segment resolution according to the baseline, peak cardiac troponin I (cTnI), cTnI after 24 hours, progression to cardiogenic shock after primary PCI and 30-day all cause mortality. ST segment resolution was measured from digitalized ECG recordings using digital calipers by a single non invasive cardiologist who was blinded to group assignment. The lead with the highest ST elevation on initial ECG was identified and ST elevation measured 40 ms after QRS, using TP segment as baseline.[17]ST segment elevation was measured in the same lead from the second ECG recorded on admission to the coronary care unit following primary PCI. Based on these two measurements, percent of change was calculated.

Prespecified subgroup analysis included gender (male, female), age (□65 years, >65 years), infarct related artery (left anterior descending, left circumflex, right coronary, side branch), time from symptom onset to prehospital UFH administration (<2 hours, 2–4 hours, >4 hours) and time from prehospital UFH administration to coronary angiography (□1 hour, >1 hour).

Additional non prespecified study endpoints were 1-year all cause mortality and primary and safety endpoints according to radial or femoral access site.

Statistical analysis

The study was designed as a superiority trial testing hypothesis that UFH pretreatment increases IRA patency at initial coronary angiography compared to current standard of care with UFH given only after coronary angiography and before primary PCI. Sample size calculation was based on primary endpoint with expected absolute difference of 11.5% in IRA TIMI 2-3 flow in favor of prehospital UFH pretreatment [7–10]. Based on this assumption, 538 patients were needed to achieve a statistical power of 80% at a two-sided significance level of 0.05. Considering expected dropout of approximately 2.5% in each group, total sample size was increased to 600. Sample size calculations were made by Sealed Envelope Ltd. 2012 Power

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Calculator for Binary Outcome Superiority Trial Web Application (https://www.sealedenvelope.com/power/binary-superiority/).

Numerical data are shown as mean and standard deviation or median with 25th and 75th interquartile ranges (IQR). Categorical data are shown as numbers and proportions in percentages. Between-group comparisons for numerical variables were performed using unpaired t-tests for normally distributed variables and Mann–Whitney U tests for non-normally distributed variables. Categorical variables were compared by Fisher's exact test or chi-square test. All statistical tests were two-sided, and a significance threshold (alpha) of 0.05 was used for primary analyses.

Primary analysis was performed according to the intention-to-treat. Additional sensitivity analyses were performed in a "per-protocol" and "as treated" for evaluation of data robustness. (Supplementary appendix). "Per protocol" population was defined as patients who fulfilled all inclusion and exclusion criteria, received treatment as randomized, underwent coronary angiography, had STEMI, and had no protocol deviations affecting the primary outcome. "As-treated" population was defined according to the actual treatment. Effect sizes regarding secondary outcomes are presented as relative risks with corresponding 95% confidence intervals (CI), calculated using generalized linear models with a log link and binomial distribution. Forest plots of the relative risk for the primary outcome with 95% CI were computed for prespecified subgroups. Corresponding p-values for interaction were derived from logistic regression models including interaction terms between treatment and each subgroup variable. An overview of data availability, eligibility, and reasons for non-assessment is provided in Supplementary Table S11. SPSS 22.0.0.0 was used for statistical analysis.

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Results

From March 10, 2022 to February 5, 2025, among 1162 consecutive STEMI patients referred for primary PCI at the University Medical Center Ljubljana (Slovenia), 600 (52%) were randomized. Because of two randomization errors and inability to obtain inform consent in 5 patients, 298 patients were ultimately enrolled to UFH pretreatment group and 295 in the control group (Figure 1). There was no significant difference in age, gender, body mass index, cardiovascular risk factors, previous history of atherosclerotic events, revascularization procedures and medical therapy (Table 1). There was also no difference between UFH pretreatment and control group in previous treatment with acetylsalicylic acid (18% vs. 22%), P2Y12 inhibitors (3% vs. 1.6%) and anticoagulants (3% vs. 4%). The delays between symptom onset to prehospital FMC (70 vs 66 minutes; p=0.986) and from FMC to cath lab arrival were also comparable. Median time from prehospital UFH administration to coronary angiography was 60 min (25th and 75th IQR 47 - 55 min) and the average prehospital dose of UFH was 97 IU/kg (25th IQR 92 IU/kg; 75th IQR 100 IU/kg).

Radial access was used in 77.4% in the UFH pretreatment group and in 79.8% in control group (p=0.473) (Table 1). Obvious IRA was documented in >95% without significant difference between the groups. Primary PCI with IRA stenting was performed in 97% in the pretreatment group and 94.6% in standard group (p=0.153). Periprocedural medication included eptifibatide, canglerol and one of the oral P2Y12 inhibitors without significant differences between the groups. Cumulative dose of UFH including prehospital UFH was significantly greater in the pretreatment group (163 vs 92 IE/kg; p>0.001).

TIMI 2-3 in IRA at initial coronary angiography was documented in 43% in UFH pretreatment group and 27% in the control group (RR 1.59 [95% CI 1.27-1.98]; p<0.001) (Figure 2A and Table 2). BARC 3-5 bleeding was documented in 2.4% in the UFH pretreatment group and 2.0% in the control group (RR 1.16 [95% CI 0.39-3.45]; p=0.789)

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(Figure 2B and Table 2). These findings were consistent with "per protocol" (Supplementary appendix, Table S6) and "as treated" analyses (Supplementary appendix, Table S7).

Postprocedural TIMI 3 flow was documented in 81.1% in the UFH pretreatment group and in 80.8% in the control group (p=0.863) (Table 2). Early ST-resolution was better in UFH pretreatment group (65% vs 59%; p=0.047). There was no significant difference in peak cTnI between the groups. However, cTnI at 24 hours was significantly decreased in UFH pretreatment group compared to the control group (30.357 vs 41.795 ng/L; p=0.036). There was no significant difference in incidence of cardiac arrest, progression to cardiogenic shock and 30-day all cause mortality between the groups.

Prespecified subgroup analyses are shown in Figure 3. The relative risk estimates were directionally consistent across subgroups defined by sex, age, culprit artery, symptom-to-heparin time, and time from heparin administration to coronary angiography. Formal tests for interaction were not statistically significant for any subgroup (all p for interaction >0.05), indicating no evidence of heterogeneity of treatment effect.

One-year all cause mortality was 4.1% in UFH pretreatment group and 2.8% in control group (p=0.397). Primary efficiacy endpoint was in favour of UFH pretreatment also when patients were stratified according to radial (RR 1.58 [CI 95% 1.21-2.05], p = 0.001) or femoral access (RR 1.73 [CI 95% 1.04-2.88], p = 0.039). BARC 3-5 bleeding was comparable in UFH pretreatment and control groups in both, radial (RR 1.44 [CI 95% 1.00-2.07], p = 0.064) and femoral access (RR 0.97 [CI 95% 0.59-1.59], p = 1.000).

Discussion

The main finding of our study is that UFH administration at the dose of 70-100 IE/kg at prehospital FMC in STEMI patients with direct transfer to primary PCI significantly improves IRA patency from 27% to 43% at initial coronary angiography without increasing the risk of

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significant bleeding. Since UFH nowadays represents a standard anticoagulation drug during primary PCI, administration at prehospital FMC with additional adjustments according to ACT before primary PCI seems very reasonable although unequivocal proof of reduced infarct size and improved clinical outcome is still missing.

The rate of IRA patency after prehospital UFH in our study was comparable to pretreatment with bivalirudin[4] or abciximab[18] and notably higher than after ticagrelor[5,6]. It is important to notice, however, that pretreatment with these agents may be associated with excess of bleeding [5,18–20] which was, importantly, not a case in our study.

Our findings are in accordance with the recent HELP-PCI randomized trial from China which showed significantly improved IRA-TIMI 3 flow from 17.6% to 23.5%[13]. However, when pooling together TIMI 2 and 3 flow, the benefits in HELP-PCI (32.2% vs 27.9%) are less obvious than in our patients (43% vs 27%). This difference is best explained by shorter delay from symptom onset to FMC in our patients (70 vs 161 minutes) which is likely to be associated with less organized coronary thrombus more prone to UFH dissolution.

Although statistically significant treatment effects were observed in certain prespecified subgroups, there was no evidence of heterogeneity across the subgroups with non significant p-value for interaction. These findings therefore do not provide evidence of differential treatment effect and may be at best hypothesis generating.

Limitations

Primary endpoint, IRA patency at initial coronary angiography, was evaluated by a single experienced interventional cardiologist who was blinded to UFH assignment and not by a core lab or another independent interventional cardiologist. We addressed only IRA patency without measuring infarct size although significantly better ST resolution and lower cTnI at 24 hours in UFH pretreatment group may pinpoint to smaller infarct size. Unfortunately, our protocol did not specify more troponin measurements which would enable calculation of area under the

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curve to better estimate an infarct size. Furthermore, echocardiography during the follow up, which could provide a signal for better left ventricular function in UFH pretreated patients, was not one of the study endpoints. Our study was underpowered to address clinical endpoints such as 30-day and 1-year mortality as well as incidence and degree of heart failure which may be more sensitive indicator to show potential benefits of UFH pretreatment. Last but not least, our study excluded high risk STEMI patients such as late presenters, comatose survivors of cardiac arrest and patients with cardiogenic shock.

Conclusions

In patients with STEMI undergoing primary PCI in a high volume "24-7" primary PCI center surrounded by contemporary STEMI network, pretreatment with UFH at prehospital FMC improves IRA patency at initial coronary angiography without increasing risk of significant bleeding. Such treatment, which is safe and cheap, has a potential to reduce infarct size and improve clinical outcome.

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Disclosures

None of the authors have any conflicts of interest regarding this trial.

Supplemental Materials

Checklists

Supplementary appendix

Tables S1 – S8

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Table 1. Patient characteristics, prehospital treatment and periprocedural features in STEMI patients undergoing pretreatment with unfractioned heparin (UFH) and control group without pretreatment

	UFH pretreatment (n=298)	No UFH pretreatment (n=295)	p
Age, years	64.2±11.7	63.0±11.6	0.186
Male	215 (72%)	225 (76%)	0.215
Body mass index	27.8±4.3	28.2±4.2	0.257
Hypertension	151/298 (51%)	159/295 (54%)	0.431
Diabetes	52/298 (17%)	49/295 (17%)	0.786
Hypercholesterolemia	98/298 (33%)	101/295 (34%)	0.727
Curent smoking	127/298 (43%)	117/295 (41%)	0.464
Previous MI	30/298 (10%)	38/295 (13%)	0.282
Previous stroke	15/298 (5%)	11/295 (4%)	0.438
PAD	11/298 (4%)	13/295 (4%)	0.658
Previous PCI	36/298 (12%)	45/295 (15%)	0.260
Previous CABG	2/298 (0.7%)	2/295 (0.7%)	1.000
ACE inhibitor/Sartan	117/298 (39%)	132/295 (45%)	0.748
Statin	77/298 (26%)	79/295 (27%)	0.796
Beta blocker	67/298 (23%)	63/295 (21%)	0.740
Ca channel blocker	53/298 (18%)	61/295 (21%)	0.371
Furosemide	5/298 (2%)	4/295 (1%)	1.000
Acetylsalicilic acid	53/298 (18%)	66/295 (22%)	0.163
Clopidogrel	6/298 (2%)	3/295 (1%)	0.505
Prasugrel	2/298 (0.7%)	1/295 (0.3%)	1.000
Ticagrelor	1/298 (0.3%)	1/295 (0.3%)	1.000
Anticoagulation	8/298 (3%)	13/295 (4%)	0.275
Prehospital treatment			
Symptoms to FMC, min*	70 (35-135)	66 (35-120)	0.986
FMC to cathlab, min*	69 (50-95)	66 (49-100)	0.853
Symptoms to cathlab, min*	145 (107-210)	150 (104-220)	0.814
Acetylsalicilic acid at FMC	296/298 (99.3)	294/295 (99.7)	0.569
UFH pretreatment at FMC	291/298 (97.7)	5/295 (1.7)	<0.001
Primary PCI			
Coronary angiography	296/298 (99.3)	292/295 (99.0)	0.645
Radial access	229/296 (77.4)	233/292 (79.8)	0.473
Obvious IRA	285/296 (96.3)	280/292 (95.9)	0.806
LM	6 (2.1)	2 (0.7)	
LAD	97 (34.0)	120 (42.9)	
LCX	35 (12.3)	32 (11.4)	
RCA	121 (42.5)	113 (40.4)	
Side branch	26 (9.1)	13 (4.6)	
Multivessel disease	108/296 (36.5)	107/292 (36.6)	0.968
PCI with stenting	287/296 (97.0)	280/296 (94.6)	0.153
Total UFH, IE/kg*	163 (146-181)	92 (83-100)	<0.001
Eptifibatide	44/287 (15.3)	43/280 (15.4)	0.993
Cangrelor	13/287 (4.5)	16/280 (5.7)	0.522
Oral $P2Y_{12}$ inhibitor			0.282
Clopidogrel	43/287 (15.0)	32/280 (11.4)	

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Ticagrelor	156/287 (54.4)	169/280(60.4)	
Prasugrel	88/287 (30.7)	79/280 (28.2)	
Hemostasis at puncture site			0.102
Radial band	228/296 (77.0)	232/292(79.5)	
Femoral closure device	49/296 (16.6)	53/292 (18.2)	
Femoral manual compression	10/296 (3.4)	3/292 (1.0)	
Radial band and femoral closure device	8/296 (2.7)	3/292 (1.0)	

FMC=First prehospital medical contact; IRA = infarct related artery; LM=left main; LAD=Anterior descending artery; LCX=Left circumflex artery; RCA=Right coronary artery; MI=Myocardial infarction; PAD=Peripheral arterial disease
*Median, 25th and 75th interquartile range

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Table 2. Study endpoints

	UFH pretreatment N=298	No UFH pretreatment N=295	Relative risk (95% CI)	p
Primary endpoint				
Initial TIMI 2/3	126/296 (42.6)	78/292 (26.7)	1.59 (1.27-1.98)	<0.001
Initial TIMI flow				<0.001
TIMI 0	137/296 (46.3)	191/292 (65.4)		
TIMI 1	33/296 (11.1)	23/292 (7.9)		
TIMI 2	58/296 (19.6)	38/292 (13.0)		
TIMI 3	68/296 (23.0)	40/292 (13.7)		
Safety endpoint				
BARC 3-5 bleeding	7/297 (2.4)	6/295 (2.0)	1.16 (0.39-3.45)	0.789
BARC 0-5 **				0.077
No bleeding	219/297 (73.7)	236/295 (80.0)		
BARC 1	51/297 (17.2)	38/295 (12.9)		
BARC 2	20/297 (6.7)	15/295 (5.1)		
BARC 3a	3/297 (1.0)	2/295 (0.7)		
BARC 3b	1/297 (0.3)	1/295 (0.3)		
BARC 3c	1/297 (0.3)	0/295 (0.0)		
BARC 4	2/297 (0.7)	3/295 (1.0)		
BARC 5	0/297 (0.0)	0/295 (0.0)		
Final TIMI flow				0.863
TIMI 0	3/296 (1.0)	4/292 (1.4)		
TIMI 1	3/296(1.0)	5/292 (1.7)		
TIMI 2	50/296 (16.9)	47/292 (16.1)		
TIMI 3	240/296 (81.1)	236/292 (80.8)		
ST-resolution,%	65 (42-88)	59 (30-80)		0.047
Troponin I 24h, ng/L*	30.357 (10.272-66.828)	41.795 (17.550-71.396)		0.036
Peak Troponin I, ng/L*	43.126 (13.133-96.592)	46.971 (20.152-94.839)		0.318
Cardiac arrest	11/298 (3.7)	14/295 (4.7)		0.523
Shock	46/298 (15.4)	41/295 (13.9)	1.11 (0.75-1.64)	0.597
Death at 30 days	7/294 (2.4)	7/282 (2.5)	0.96 (0.34-2.70)	0.937

*Median, 25th and 75th interquartile range
** Mann-Whitney U test comparing ordinal BARC bleeding severity

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Figure Legends

Figure 1. Study flowchart

Figure 2. Primary efficacy and safety endpoints in patients with UFH pretreatment and control group

IRA TIMI 2-3 flow at initial coronary angiography (A); BARC 3-5 bleeding (B)

Figure 3. Forest plot with relative risk (RR) and 95% confidence intervals (CI) for primary endpoint (TIMI 2-3 at initial coronary angiography) in prespecified subgroups

No UFH group was used as common reference category for estimated RR.

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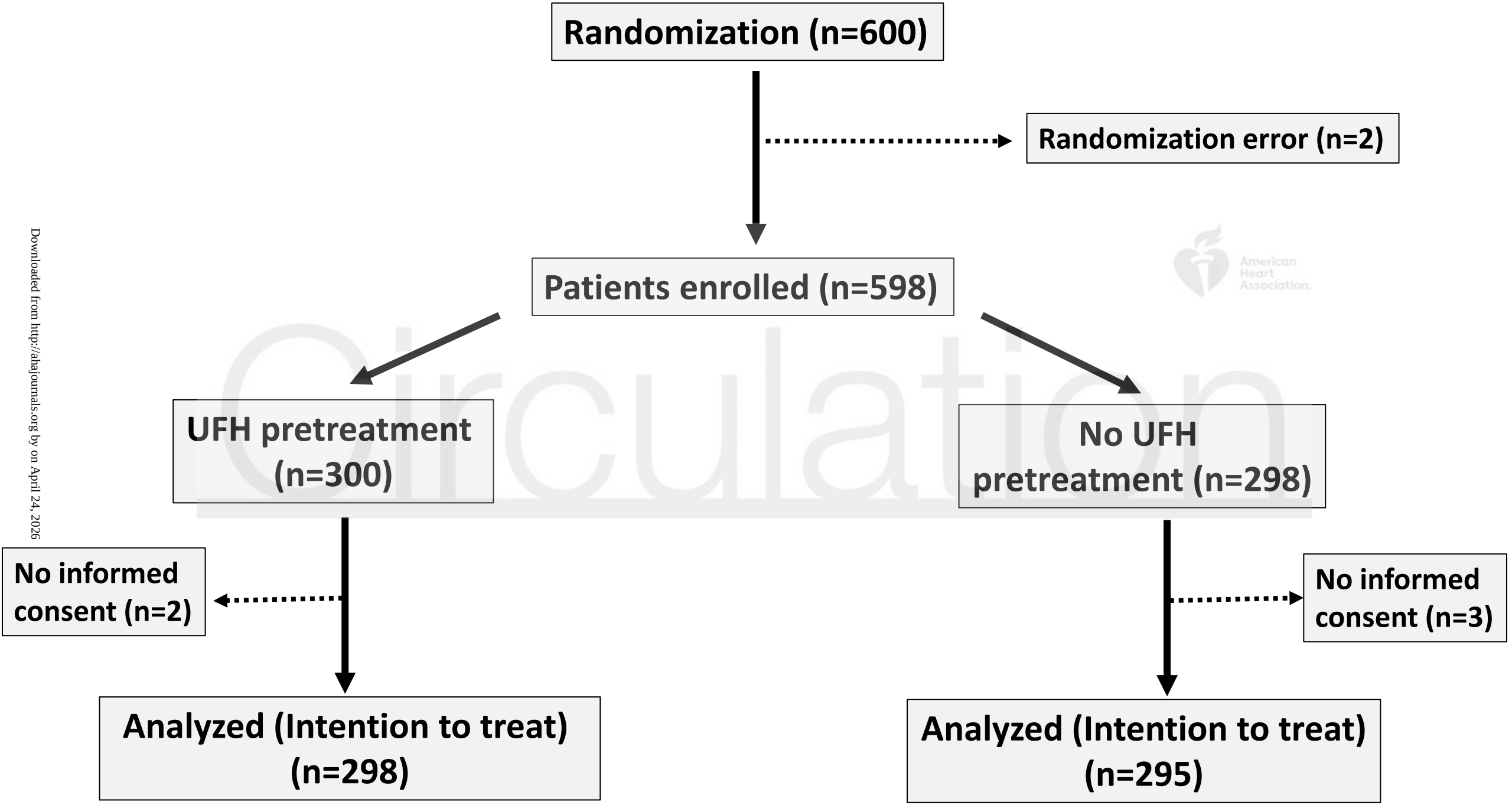

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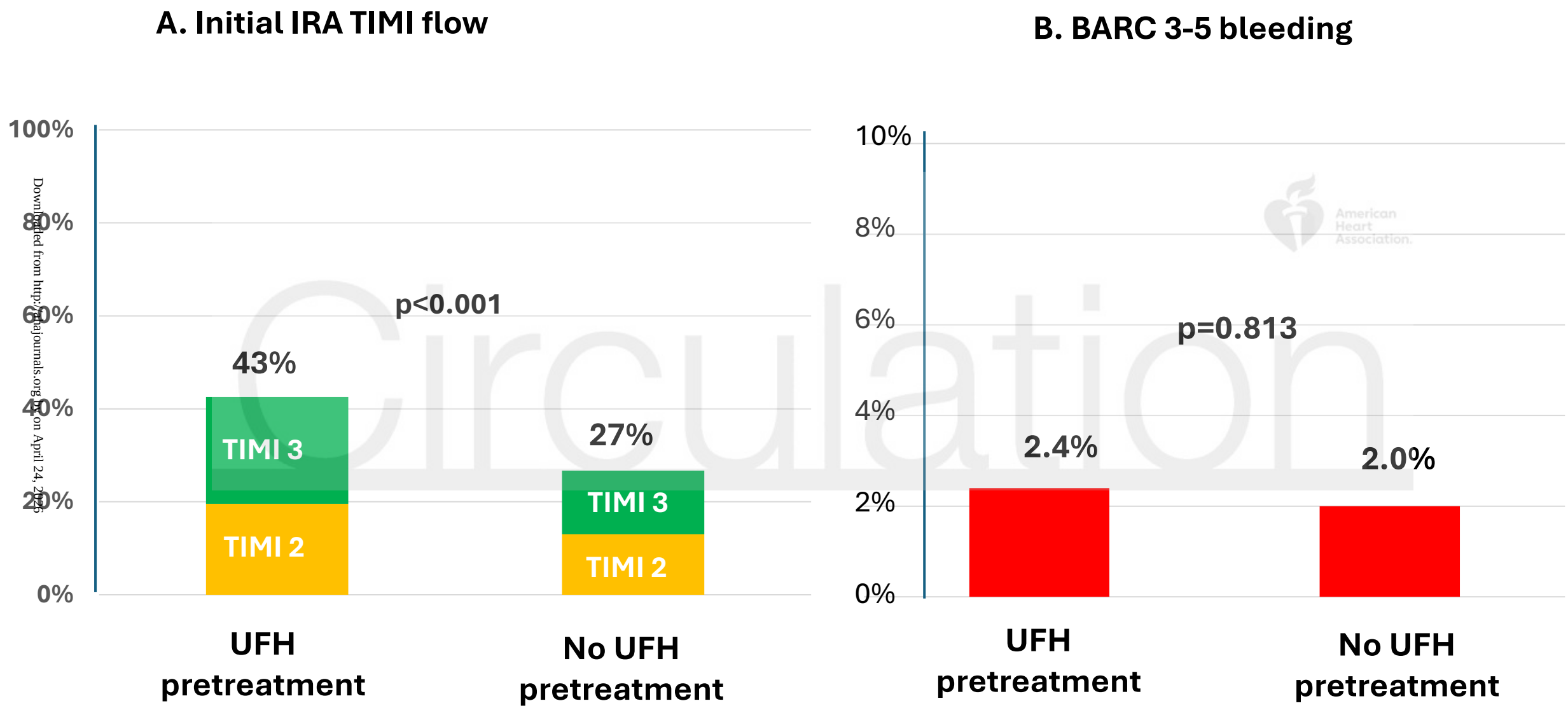

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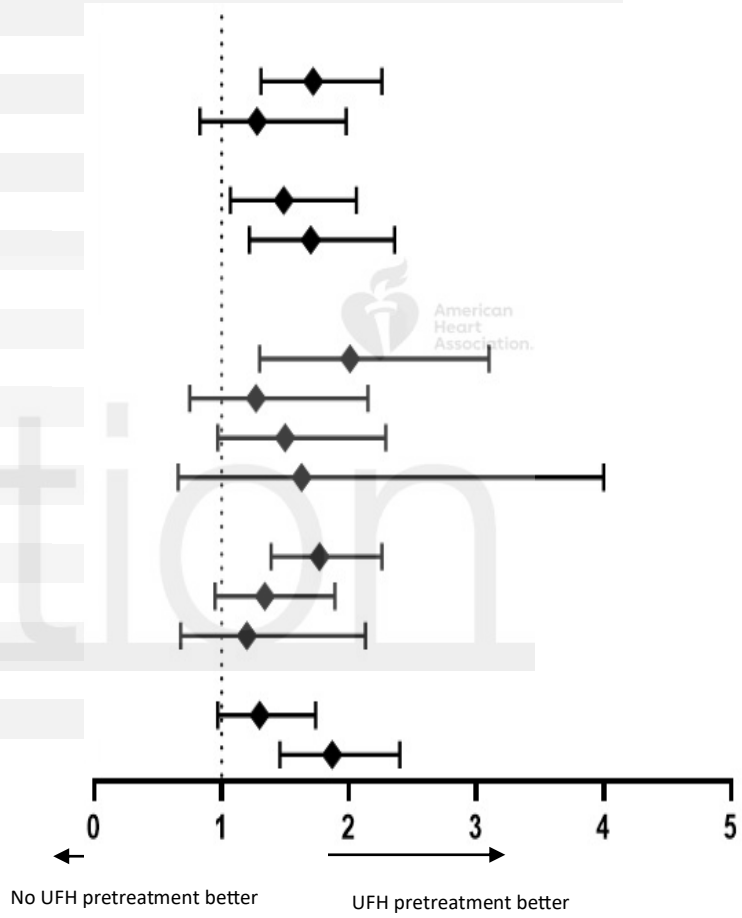
Subgroup	Early heparin	Control	RR (95% CI)	p	p for interaction
Sex					0.273
Male	93/214 (43.5)	56/222 (25.2)	1.72 (1.31-2.26)	**<0.001**	
Female	33/82 (40.2)	22/70 (31.4)	1.28 (0.83-1.98)	0.260	
Age					0.468
<65 years	61/158 (38.6)	42/162 (25.9)	1.49 (1.07-2.06)	**0.015**	
≥65 years	65/138 (47.1)	36/130 (27.7)	1.70 (1.22-2.36)	**0.001**	
Culprit artery					0.745
LM	5/6 (83.3)	0/2 (0.0)		0.035	
LAD	39/97 (40.2)	24/120 (20.0)	2.01 (1.30-3.10)	**0.001**	
LCX	18/35 (51.4)	13/32 (40.6)	1.27 (0.75-2.15)	0.376	
RCA	40/121 (33.1)	25/113 (22.1)	1.50 (0.97-2.29)	0.062	
Side branch	13/26 (50.0)	4/13 (30.8)	1.63 (0.66-4.00)	0.254	
Symptoms to heparin (time - h)					1.000
<2	87/184 (47.3)	78/292 (26.7)	1.77 (1.39-2.26)	**<0.001**	
2-4	30/84 (35.7)		1.34 (0.95-1.89)	0.108	
>4	9/28 (32.1)		1.20 (0.68-2.13)	0.537	
Heparin to coronary angiography (time - h)					1.000
≤1	50/144 (34.7)	78/292 (26.7)	1.30 (0.97-1.74)	0.084	
>1	76/152 (50.0)		1.87 (1.46-2.40)	**<0.001**	



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